because histamine is tightly bound within the cell boundaries of the circulating basophils. Further studies of total blood histamine as well as plasma histamine levels and their correlation with gastric secretory rates in patients with myeloproliferative disease are needed. Determining levels of histamine, evaluating gastric secretory status and obtaining x-ray films of the upper gastrointestinal region in patients with myeloproliferative diseases should be given higher priority.

Summary

The mast cell (tissue) and basophil (circulating) are known to have high concentrations of histamine. Proliferation of mast cells (systemic mastocytosis) often results in hyperhistaminemia with resultant pharmacologic effects (pruritus, urticaria and the like). Similarly, proliferation of basophils (myeloproliferative diseases) is associated with hyperhistaminemia. It is odd that reports of pharmacologic effects of histamine on target organs (skin, lungs, heart and stomach) have been reported in rare instances only. This case of chronic myelogenous leukemia is the second that has been reported involving histamine stimulation of gastric acid secretion and peptic ulceration of a magnitude similar to the acid secretion resulting from hypergastrinemia. It is the first case showing adequate control of the hyperacid secretory state by cimetidine treatment. It is possible that pharmacologic effects of hyperhistaminemia in the myeloproliferative diseases is more common than the literature indicates.

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Necrotic Arachnidism

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ARACHNIDISM IN NORTH AMERICA was first discussed in the medical literature of the United States in 1872.[1] It was not until 1957, however, that the first article discussing Loxosceles species of spiders as the probable cause of necrotizing bites in the United States was published.[2] Since then the number of presumed and proved cases of necrotic arachnidism has greatly increased. The cases reported have ranged from insignificant blebs,[3] through troublesome necrotic lesions, to serious necrosis complicated by hemolytic anemia, diffuse intravascular coagulation and death.[4-6]

Until about ten years ago necrotic arachnidism was thought to be a problem only in the midwestern United States, but then reports of similar lesions from southern and southwestern states began to appear.[7] The first case in Mississippi for example, was recorded in 1962, but by 1971 a total of 31 necrotic spider bites were reported there.[8] By 1966 necrotic arachnidism had occurred as far west as Los Angeles, as far north as Indiana and as far south as Baja California.[9] Dr. Findlay Russell of the University of Southern California, Department of Neurological Research, has recorded about ten cases of such bites in Southern California. With its increased incidence, knowledge of the natural history, physiology, diagnosis and treatment of this condition is becoming more important to physicians throughout the United States.

Report of a Case

A 23-year-old man awoke, after sleeping on the couch at his sister's house, with sudden pain in his right ankle. He tried to walk but fell be-

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cause of pain and dizziness. During the day he noted widespread muscle and joint pain which began in the right leg and thigh; nausea, fever and chills; tremor (greater in the arms); swelling and redness of the right foot, and a vesicle on the right ankle. These symptoms worsened.

The man went to the emergency room at the San Bernardino County Medical Center 12 hours after the symptoms began. A small vesicular lesion surrounded by 3 to 4 cm of erythema and induration was noted. It was felt that the cause was a spider bite. He was given medication for pain and sent home.

On his return 40 hours later the patient said that pain in his hip and shoulder joints was severe, as was pain at the site of the lesion. He was obviously distraught and there was a coarse tremor in the arms. Blood pressure was normal, temperature was 38.5°C (101.3°F) and pulse rate was 110.

On physical examination, the abdomen was mildly tender to palpation. There was no swelling, erythema, effusion or increased pain on palpation of the painful and stiff joints. The muscles, especially in the right thigh, were notably tender. On the lateral aspect of the ankle there was a 0.75 cm bullous lesion filled with clear fluid and layered white matter, surrounded by an irregular area measuring 8 cm by 15 cm of erythema and induration. The foot was held in plantar flexion and there was a pronounced decrease in the motion of all toes. Mild lymphadenopathy was found in the right inguinal region.

Because the patient was reluctant to be admitted to hospital, cloxacillin (Tegopen), 500 mg given orally every six hours, was prescribed and he was allowed to return home, with instructions to elevate his right foot. He was asked to return in 24 hours, or sooner if the lesion became worse. Specimens for complete blood count, analysis of urine and culture of the aspirate from the vesicle were obtained.

The patient returned 24 hours later, 78 hours after the onset of pain and erythema. There was a notable change in the appearance of the right foot (see Figure 1). The skin was taut with edema and induration, was slightly erythematous and was fixed in plantar flexion. In addition to the primary bulla, there were two adjacent irregular bullae, each about 3 cm in diameter. The right leg was swollen and erythematous up to the knee. The lateral part of the ankle was mottled with superficial hemorrhage, blebs, nonperfused

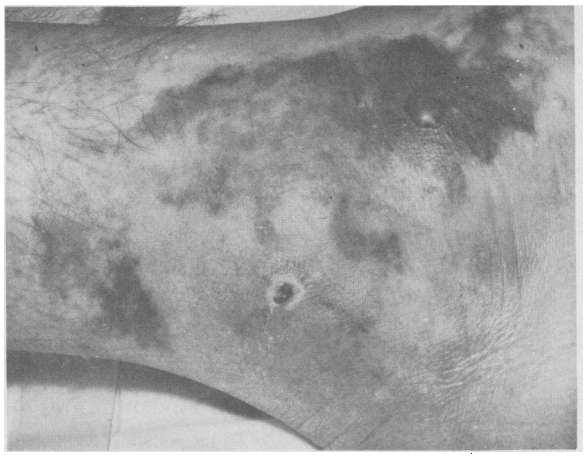

Figure 1.—Erythema, blebs, hemorrhage and ischemia occurring 78 hours after onset of symptoms.

skin and pronounced erythema. The pain was excruciating. Systemic symptoms of tremor, fever, nausea, anorexia and myalgia, although improved, were still present. The joint pain had become worse and walking was impossible. The leukocyte count was 19,400 per cu mm with 81 percent polymorphonuclear leukocytes, 16 percent bands, 7 percent lymphocytes, 1 percent monocytes and no eosinophils. Erythrocyte sedimentation rate was 36 mm per hour, blood urea nitrogen level was 11 mg per dl, creatinine level was 1.1 mg per dl, and analysis of urine showed 1+ proteinuria and acetone. The culture of the aspirate showed heavy growth of β-hemolytic streptococci, group A.

The patient was admitted to hospital with the diagnosis of reaction to insect bite or arthropod envenomation and cellulitis. Administration of penicillin G, 2 million units given every four hours intravenously, was started. Treatment with steroids was begun, but discontinued because it had been started relatively late and because the cultures were positive. By the morning of the fifth day, an eschar measuring 4 cm by 6 cm had formed in the area of hemorrhage (see Figure 2). That night the eschar was debrided and approximately 20 ml of purulent material was collected. The dermis had been undermined and this was debrided.

The following morning the tremor was gone, and muscle and joint pain were remarkably improved. The lesion continued to expand. Three days later necrotic tissues were debrided down to the musculoaponeurotic tissues, exposing the Achilles tendon posteriorly. No tendons, nerves or vessels were damaged (see Figure 3). Motion of the right ankle improved shortly afterward.

Saline wet-to-dry dressings and sutilains ointment (Travase) were used to promote granulation and prevent accumulation of necrotic tissue. Sharp debridement was done as indicated.

Further undermining of the dermis for 2 to 3 cm beyond the edges of the skin was noted 23 days after presentation. These areas were debrided and Nu-Gauze wicks were placed. Shortly after, a split-thickness meshed skin graft and a protective plaster cast were applied. On examination one week later and six weeks after presentation, there was a complete take of the graft and a full range of motion of the foot and ankle (see Figure 4).

Discussion

There are at least ten different species of Loxosceles spiders in the United States. Six of them have been proved experimentally to cause

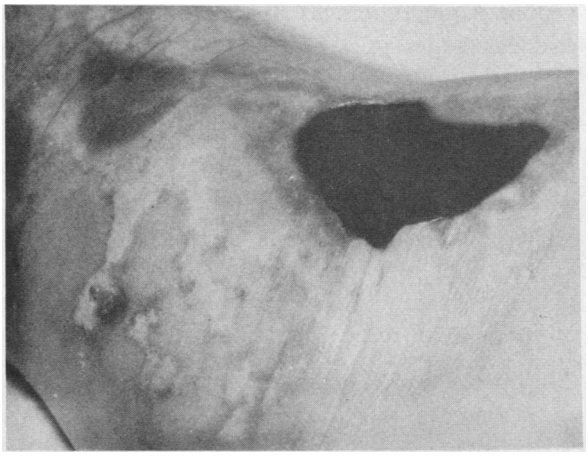

Figure 2.—Eschar formation 96 hours after initial symptoms.

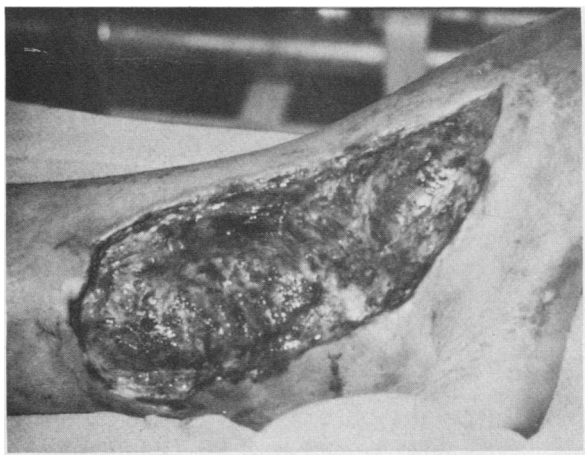

Figure 3.—Final debriding before skin graft. Note extensive skin and fatty necroses. Muscle, tendon, major nerves and vessels were spared.

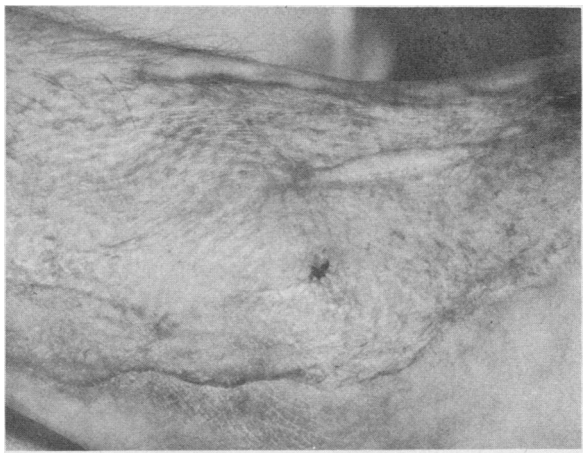

Figure 4.—Skin graft six months after original lesion began to form.

necrotic arachnidism: Loxosceles reclusa, the first to be discussed in North American literature and the best studied[2] (see Figure 5); Loxosceles laeta, the common cause of necrotic arachnidism in South America; Loxosceles unicolor, first discovered in California and Arizona in 1969,[10] but reported as early as 1961 in Texas;[5] Loxosceles deserta,[10] subsequently found to have caused many cases in Southern California previously attributed to L. unicolor and Loxosceles arizonica;[11] and Loxosceles refescens.

Loxosceles spiders have the same general body shape as black widow spiders. There is a typical violin marking over the septal thorax that accounts for the common name, violin spider. In some species this marking is so faint that it may easily be overlooked. These spiders vary in size from 6 to 20 mm, and in color from yellow to dark brown. Loxosceles species seem to prefer dark quiet places, often indoors—such as in undisturbed clothing, bedding, furniture and storage sheds. They are nocturnal feeders and run with amazing speed in the face of adversity, provided there is an avenue of escape. Unlike black widow spiders, both male and female Loxosceles spiders can cause serious envenomation.

The Venom

In addition to similarities in habitat, at least three—and probably more—of Loxosceles species have similar venom. Venom of Loxosceles spiders has been shown to contain many components, including collagenase, dipeptides, esterase, protease, deoxyribonuclease, ribonuclease, phospholipases and hyaluronidase.[12] Wright, Elgert and Campbell, however, could find only hyaluronidase

and esterase. They found that inactivation of hyaluronidase in the venom did not stop dermonecrosis.[13]

Later work by Elgert and co-workers showed that rabbits could be immunized against Loxosceles spiders by using increasing doses of venom. Antivenom produced in this way prevented dermonecrosis in animals injected with venom.[14] In a comparative study by immunodiffusion and electrophoresis of three Loxosceles species, antigenic similarity of the venom of each species was found.[15] This accounts for the fact that L. laeta antivenom decreases necrosis from bites of other Loxosceles species. Evidence shows that venom-complement interaction causes pronounced infiltration of polymorphonuclear leukocytes into surrounding tissues. In experimental animals made either neutropenic or hypocomplementemic, edema and necrosis did not develop at envenomation sites.[16] Lysis of polymorphonuclear leukocyte lysosomes that contain kinin-forming enzyme activity, mast cell rupturing activity and vasoactive cationic proteins, plus acid and neutral proteins, may account for a large part of the tissue damage (see Figure 6).

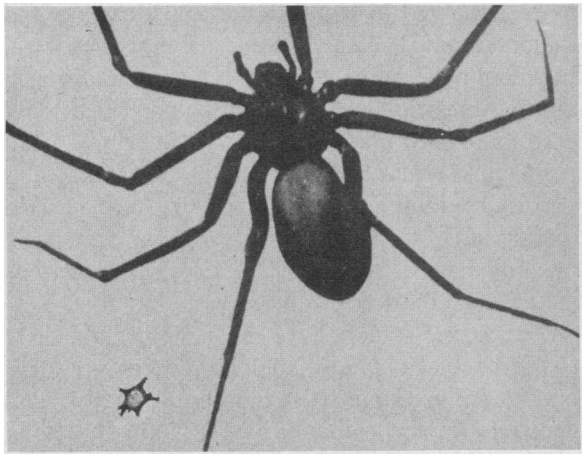

Figure 5.—Loxosceles reclusa spider.

In contrast to the well-studied mechanism of local necrosis, that of systemic hemolytic reactions remains unclear. Denny, Dillaha and Morgan found that venom alone had a hemolytic effect on human red cells *in vitro*. The hemolytic component in the venom was heat labile, but not complement dependent. Lecithin incubated with venom breaks into two components, which suggests that venom contains a lysolecithin that hemolyzes red cells.[17] Smith and Micks contradicted these findings. *In vitro* studies with extracts of venom, cephalothoraces and abdomens from Loxosceles resulted in complete hemolysis of red cells exposed to abdomen extract, partial hemolysis to extract of cephalothoraces and no hemolysis of red cells in contact with venom alone. The hemolytic process occurred at 37°C and was greatest with L. rufescens.[15] Variation in results of experiments relating to hemolysis may be due to different methods of preparing the extracts, contamination with saliva of mouth parts or by variation in mammalian red cell physiology.

Diagnosis and Treatment

In the case presented, there was a moderately severe reaction to the spider bite. Both humans

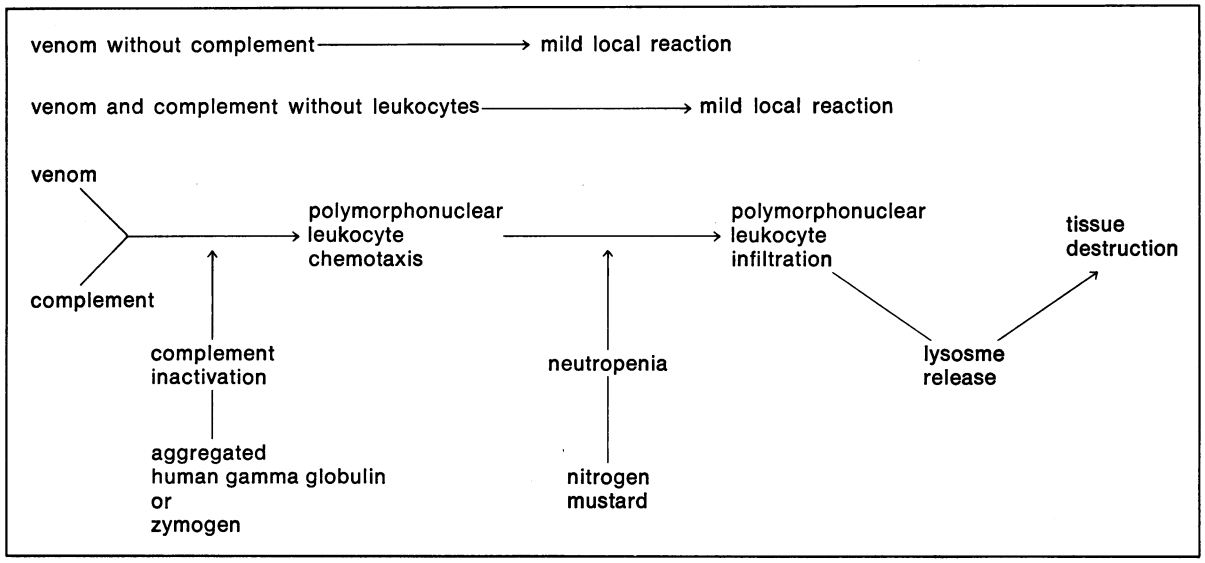

Figure 6.—Mechanism of injury.

and animals have the same general progression of symptoms, beginning with bleb formation and erythema at the site of the bite; followed by increasing pain, edema and erythema, and finally resulting in ischemia with blanching and eschar formation. Symptoms may, however, vary from negligible to fatal.

Early diagnosis and evaluation are necessary for proper treatment. Harves and Millikan note that severe bites are marked by bullae formation, pain and ischemia within the first six to eight hours. If these symptoms do not occur, treatment is probably unnecessary.[12] If no spider is found, necrotic archnidism should be considered a possible diagnosis when someone presents with a discrete bleb formation on an erythematous base and an inordinate amount of pain. Some physicians recommend immediate excision of such lesions down to and including the first fascial plane, but it is understandable that excision is often delayed, especially because proof—the spider—is seldom seen. Hershey and Aulenbacher recommend excision after the eschar has formed and note that erythematous tissues should not be excised.[18] Medical treatment may be helpful, pending excision of the eschar. Russell suggests immediate initiation of a high dose of steroids within the first eight hours after the bite.[19] Findings from studies in animals indicate that administration of steroids is not helpful.[20] However, it is tempting to think that steroid therapy would be efficacious in lesions that are primarily mediated by inflammatory processes. Dexamethasone, 4 mg administered intramuscularly every six hours, is suggested for acute phases.

The almost inevitable secondary infection should be treated appropriately. Culture of the lesion in the case discussed grew β-hemolytic streptococci, group A. Other authors have noted frequent infections with resistant and opportunistic organisms. These were related to the use of prophylactic antibiotics and to the debilitated condition of the patients.[18] Russell also recommends using an oxygen chamber made from a large plastic bag, tape and an oxygen-flow catheter (if no oxygen chambers are available). In addition, Russell advises cleaning the lesions three times a day with aluminum acetate solution and painting the lesions with triple dye after each cleansing. Others have obtained good results with enzymatic debridement, using fibrinolysin and combined bovine desoxyribonuclease ointment (Elase). Sutilains ointment (Travase) was used in the case reported here, and resulted in good formation of granulation tissue and maintenance of a nonnecrotic wound.

Most authors agree that surgical excision of the eschar is the definitive treatment. The earlier the lesion is excised, the sooner systemic as well as localized signs resolve. Usually, fever, joint and muscle pain, anorexia, and local edema and erythema improve notably shortly after excision. The usual course is destruction of a well-demarcated area of dermis and underlying fat, with sparing of muscular and neurovascular structures. After the area of skin is delineated, further necrosis of fat causes undermining around the skin margins. These areas must be carefully debrided. After the necrosis is arrested and a good bed of granulation tissue is formed, a skin graft should be applied.

Conclusion

Loxosceles spiders are expanding their range of habitation, and physicians in the states where these spiders used to be rare should become more aware of the problem. Symptoms that indicate that a Loxosceles bite may be severe include early bleb formation, pronounced erythema and pain occurring within six hours. The mechanism is not entirely clear, but apparently involves complement-activated tissue damage. Beginning treatment promptly—including the use of steroids, local wound care and surgical debridement—should decrease severity of the symptoms and improve the outcome.

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Refer to: Rubinstein JS: Deliberate abuse of diphenoxylate hydrochloride, a schedule V narcotic. West J Med 131: 148-150, Aug 1979

Deliberate Abuse of Diphenoxylate Hydrochloride, a Schedule V Narcotic

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DIPHENOXYLATE is a meperidine congener frequently prescribed in the treatment of diarrhea. The drug is available in both tablet and liquid form (Lomotil, Colonil); each tablet and each 5 ml dose of the liquid contains 2.5 mg of diphenoxylate hydrochloride and 0.025 mg of atropine sulfate. Diphenoxylate hydrochloride is a schedule V narcotic.[1]

The chemical structure of diphenoxylate hydrochloride is similar to that of meperidine,[2] and the drug carries many of the risks and hazards characteristic of the opiates. Mild side effects include drowsiness, rash, dizziness, depression and nausea. Treatment of overdose or individual hypersensitivity reaction is similar to that for meperidine or morphine intoxication. Prolonged monitoring of the patient is essential because, although there might be an initial response to narcotic antagonists, life-threatening respiratory depression may occur as late as 30 hours following ingestion.[2] Several cases of accidental overdose in children have been reported.[3]

As with other opiates, the drug also has a potential for abuse. Though at therapeutic ranges (20 mg of diphenoxylate hydrochloride per day or less, in divided doses) opioid effects do not occur, doses of 40 to 60 mg at a time have been shown capable of producing a morphine-like euphoria.[4] Morphine-like addiction is also theoretically possible following prolonged use of the drug at high doses.

Recently, I encountered a case of deliberate abuse of diphenoxylate hydrochloride, and ordered a computer search of the literature for further information. Considering the frequency with which this drug is prescribed, its schedule V rating, and the great demand among abusers for its opiate congeners, it was surprising to discover that deliberate abuse of diphenoxylate hydrochloride for its subjective effects has never been reported in the literature.

Report of a Case

A 32-year-old man came to the psychiatric outpatient clinic with complaints of anxiety and depression over his inability to carry out his duties satisfactorily at work.

The patient had a long history of drug abuse, including the intravenous abuse of heroin, and at age 24 had been admitted to hospital for what he described as an inadvertent overdose. Following this experience he became "more cautious" in his use of drugs, resolved to stop using heroin; the patient broke all contact with the *street scene,* but continued to abuse pills, in particular barbiturates, as well as prescription opiates such as pentazocine and propoxyphene. In addition, the patient related that he had, over the past year, begun to abuse diphenoxylate hydrochloride, taking large doses of the drug intermittently, but never more than once or twice a week for periods of up to several weeks at a time.

The patient's first experience with the drug had been with a prescription given to his wife by her doctor as prophylaxis before an intended trip abroad. He had found the bottle of pills and, not being familiar with the drug, had looked it up in the *Physicians' Desk Reference.* He had learned that it was an opiate and, in large doses, could produce opiate-like effects. The patient enjoyed the sensation, and then began taking the drug regularly. He found that most physicians would issue a prescription for diphenoxylate hydrochloride with little question when he complained of diarrhea, even when he would specifically request the drug by name. On several occasions he informed the physician that he was about to embark on an extended trip abroad, and received large supplies of the drug. The patient would ordinarily take 60 to 100 tablets for the desired

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